UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: SECOND Peer Review of Glyphosate

CAS No. 1071-83-6
EPA Chem. Code 417300
40 CFR 180.364
TOX Chem. No.: 661A
Reg Group: List A (6B)

FROM: William Dykstra, Ph.D. William Dykstra
Toxicology Branch I (IRS)
Health Effects Division (H7509C)

and

George Z. Ghali, Ph.D. G. Ghali 8/22/91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Robert Taylor, PM 25
Fungicide-Herbicide Branch
Registration Division (H7505C)

and

Lois Rossi, Chief
Reregistration Branch
Special Review and Reregistration Division (H7508W)

The Health Effects Division Carcinogenicity Peer Review Committee convened on June 26, 1991 to discuss and evaluate the weight of the evidence on Glyphosate with particular emphasis on its carcinogenic potential. The Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based upon lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

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A. Individual in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penny Fenner-Crisp	Penelope J. Fenner-Crisp
William L. Burnam	
Karl Baetcke	
Marcia Van Gemert	Marcia van Gemert
Esther Rinde	
Hugh Pettigrew	
Marion Copley	
Lucas Brennecke	
George Ghali	

2. Peer Review Members in Absentia (Committee members who were unable to attend the discussion; signature indicates concurrence with the overall conclusions of the Committee.)

Reto Engler	
Richard Hill	—
John Quest	
Kerry Dearfield	
Yin-Tak Woo	
Jean Parker	— NONCONCUR
William Sette	
Robert Beliles	DO NOT CONCUR
Julie Du	

3. Scientific Reviewers (Committee or noncommittee members responsible for data presentation; signature indicates technical accuracy of panel report.)

William Dykstra	
Roger Gardner	9-5-91

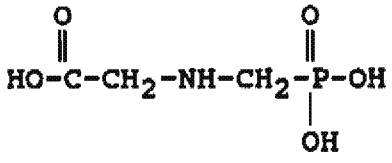
B. Background Information

Glyphosate is the isopropylamine (IPA) or sodium salt of N-(phosphonomethyl) glycine, marketed under the trade names of Roundup, Rodeo, Shackle, and Polado. Glyphosate is a wide spectrum plant growth regulator herbicide which is used to control grasses, sedges, and broadleaf weeds. It acts by the inhibition of amino acid synthesis.

Tolerances established for glyphosate and its aminomethyl phosphonic acid (AMPA) metabolite in 40 CFR 180.364 include the following:

IPA salt of glyphosate: soybeans, cotton, corn, sorghum, wheat, rice, vegetables, citrus fruits, pome fruits, stone fruits, tropical fruits, pastures, and alfalfa.

Sodium salt of glyphosate: sugarcane.



Glyphosate

On February 11, 1985, the carcinogenic potential of glyphosate was first considered by a panel (then called the Toxicology Branch Ad Hoc Committee) comprised of members of the Toxicology Branch of the Hazard Evaluation Division. The Committee, in a consensus review dated March 4, 1985, classified glyphosate as a Group C carcinogen based on an increased incidence of renal tubular adenomas in male mice. According to the consensus review, the tumor is rare, it occurred in a dose-related manner, and the incidence was outside the reported historical control range. The Committee also concluded that dose levels tested in a 26-month rat feeding study were not adequate for the assessment of glyphosate's carcinogenic potential in this species.

The kidney slides from the long-term mouse feeding study were subsequently reexamined, and one pathologist diagnosed an additional kidney tumor in control males. These findings were presented to the FIFRA Scientific Advisory Panel (SAP) which proposed that glyphosate be classified into Group D (inadequate animal evidence of carcinogenic potential). The SAP, in their meeting of February 11-12, 1986 (report dated February 24, 1986), concluded that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of

these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

HED deferred a decision on the repeat of an additional mouse oncogenicity study until the 1990 rat feeding study had been evaluated by the Peer Review Committee.

C. Material Evaluated

The material available for review consisted of a document prepared by Dr. William Dykstra summarizing major scientific and regulatory issues and relevant toxicology information, data evaluation records of a combined chronic toxicity/carcinogenicity study in rats and a carcinogenicity study in mice, the FIFRA Scientific Advisory Panel report dated Feb 24, 1986, a review of historical control data on mouse kidney tumors, a toxicology one-liner for the glyphosate data base and an OPP peer review report entitled "Consensus Review of Glyphosate" dated March 4, 1985.

D. Evaluation of Carcinogenicity Data

1. **Lankas, G. P. December 23, 1981. A Lifetime Study of Glyphosate in Rats. Unpublished report No. 77-2062 prepared by BioDynamics, Inc. EPA Acc. Nos. 247617 - 247621. MRID 00093879.**

a. Experimental Design

The lifetime feeding study in Sprague-Dawley rats at 50/sex/dose was conducted at dietary concentrations of glyphosate of 0, 30, 100, and 300 ppm. These concentrations were adjusted during the course of the study so that actual doses of 0, 3, 10, and 31 mg/kg/day in males and 0, 3, 11, and 34 mg/kg/day in female rats were maintained.

b. Discussion of Tumor Data

An increase in the incidence of interstitial cell tumors of the testes was observed in male rats. Because of the absence of a dose-response relationship, the lack of preneoplastic changes, the wide variability in the spontaneous incidence of this tumor, the similarity in incidences between the high-dose

group and the historical controls, and lack of any evidence of genotoxicity, it was concluded by the previous Peer Review Committee that the observed incidence did not reflect a carcinogenic response.

Additionally, there was the question of possible thyroid carcinomas in high-dose females. After a review of the slides by a consulting pathologist, and a reassessment of all relevant data, including the fact that no effect of treatment on tumor latency or the combined incidences of adenoma and carcinoma was apparent, the earlier Peer Review Committee concluded that the data did not demonstrate a carcinogenic response in the thyroid.

c. Nonneoplastic Lesions and Adequacy of Dosing Considerations

No effect of treatment on the incidence of nonneoplastic lesions was noted. No effects of treatment on survival, body weight gain, clinical pathology, or findings at necropsy were noted. Therefore, there is no evidence that the highest dose tested was adequate to evaluate the carcinogenic potential of glyphosate.

2. **Stout, L. D. and Ruecker, F. A. (1990). Chronic Study of glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; Sept. 26, 1990. MRID No. 416438-01; Historical Controls; MRID No. 417287-00.**

a. Experimental Design

This chronic toxicity/carcinogenicity study in the rat was submitted to the Agency as a replacement study for the 26-month 1981 chronic toxicity/carcinogenicity study in the rat. In this study, randomized groups of 60 male and 60 female young (8 weeks old) Sprague-Dawley rats were fed dietary levels of 0, 2000, 8000, or 20,000 ppm or the equivalent of 0, 100, 400, and 1000 mg/kg/day of technical glyphosate for 2 years. At 12 months, 10 animals/sex/group were sacrificed.

b. Discussion of Tumor Data

Age-adjusted, statistical analyses of the tumor data are presented. The most frequently observed tumors in this study were pancreatic islet cell adenomas in males, thyroid C-cell adenomas and/or carcinomas in males and females, and hepatocellular adenomas and carcinomas in males. The following is a discussion of each type of tumor.

i. Pancreas (Tables 1 - 3)

Low-dose and high-dose males had a statistically significant increased incidence of pancreatic islet cell adenomas.

Table 1: Glyphosate - Sprague-Dawley Male Rats, Pancreatic Islet Cell Tumor Rates* and Cochran-Armitage Trend Test and Fisher's Exact Test Results (p values).

Tumors	Dose (ppm) 0	2000	8000	20,000
Carcinomas	1/43[a]	0/45	0/49	0/48
(%)	(2)	(0)	(0)	(0)
p =	0.159	0.409(n)	0.467(n)	0.472(n)
Adenomas	1/43	8/45	5/49	7/48[b]
(%)	(2)	(18)	(10)	(15)
p =	0.170	0.018*	0.135	0.042*
Adenomas/carcinomas	2/43	8/45	5/49	7/48
(%)	(5)	(18)	(10)	(15)
p =	0.241	0.052	0.275	0.108
Hyperplasia only	2/43	0/45	3/49	2/48[c]
(%)	(5)	(0)	(6)	(4)
p =	0.323	0.236	0.526	0.649

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

[a] First carcinoma observed at week 105, dose 0 ppm.

[b] First adenoma observed at week 81, dose 20000 ppm.

[c] First hyperplasia observed at week 91, dose 20000 ppm.

[d] $p \leq 0.05$; Fisher's Exact test with Bonferoni correction.

Note:

Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Historical control data on the incidence of pancreatic islet cell adenomas from Monsanto's EHL are shown in Table 2 below.

Table 2: EHL 87122 - Historical Control Information for Histopathological Findings (All Deaths)

Terminal Necropsy Study	Months of Date	Study Length (Months)	No. Observed	No. Affected	% Affected
1	07/83	24	68	2	2.9
2	02/85	23	59	5	8.5
3	10/85	24	69	4	5.8
4	06/85	24	57	1	1.8
5	09/88	24	60	5	8.3
6	01/89	24	60	3	5.0
7	03/89	24	59	3	5.1

Committee's interpretation: Although the incidences of the pancreatic islet cell adenomas at the low-, mid- and high-dose groups exceeded the historical control range of 1.8 to 8.5 percent in male rats, there was no statistically significant positive dose-related trend in the occurrence of these tumors in males, no progression to carcinoma, and the incidence of hyperplasia was not dose-related. Therefore, the pancreatic islet cell tumors were not considered to be compound-related. It was also noted that the incidence of this lesion in the concurrent control for males was at the low end of the historical control range. The Committee concluded that the apparent statistical significance of the pairwise comparisons of the treated male groups with the concurrent control might have been attributable to this factor and not to actual carcinogenic response.

The incidences of islet cell pancreatic tumors in the earlier rat study (Bio/dynamics Project No. 77-2062) are shown in Table 3. The incidence of pancreatic islet cell tumors for the two studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

Table 3: Incidence of Pancreatic Islet Cell Tumors in Male Sprague-Dawley Rats Given Diets Containing Glyphosate for 26 Months (first rat feeding study).

Tumors	Dose (mg/kg/day) 0	3	10	30
Hyperplasia (%)	3/50 (6)	2/49 (4)	1/50 (2)	0/50 (0)
Adenomas (%)	0/50 (0)	5/49 (10)	2/50 (4)	2/50 (4)
Carcinomas (%)	0/50 (0)	0/49 (0)	0/50 (0)	1/50 (2)
Adenoma/carcinoma (%)	0/50 (0)	5/49 (10)	2/50 (4)	3/50 (6)

ii. Thyroid (Tables 4 - 6)

C-cell adenomas were slightly increased in male and female mid- and high-dose groups as shown in Tables 4 and 5. Historical control ranges for the thyroid tumors in Sprague-Dawley rats were reported as shown in Table 6.

Committee's interpretation: Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

Table 4: Glyphosate - Sprague-Dawley Male Rats, Thyroid C-Cell Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	0/54	2/55[a]	0/58	1/58
(%)	(0)	(4)	(0)	(2)
p =	0.452	0.252	1.000	0.518
Adenomas	2/54[b]	4/55	8/58	7/58
(%)	(4)	(7)	(14)	(12)
p =	0.069	0.348	0.060	0.099
Adenoma/carcinoma	2/54	6/55	8/58	8/58
(%)	(4)	(11)	(14)	(14)
p =	0.077	0.141	0.060	0.060
Hyperplasia only	4/54	1/55	5/58[c]	4/58
(%)	(7)	(2)	(9)	(7)
p =	0.312	0.176	0.546	0.601

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[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 54 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 5: Glyphosate - Sprague-Dawley Female Rats, Thyroid C-Cell Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Tests Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	0/57	0/60	1/59[a]	0/55
(%)	(0)	(0)	(2)	(0)
p =	0.445	1.000	0.509	1.000
Adenomas	2/57	2/60	6/59[b]	6/55
(%)	(4)	(3)	(10)	(11)
p =	0.031*	0.671(n)	0.147	0.124
Adenoma/carcinoma	2/57	2/60	7/59	6/55
(%)	(4)	(3)	(12)	(11)
p =	0.033*	0.671(n)	0.090	0.124
Hyperplasia only	10/57[c]	5/60	7/59	4/55
(%)	(18)	(8)	(12)	(7)
p =	0.113	0.112	0.274	0.086(n)

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[a] First carcinoma observed at week 93 at 8000 ppm.

[b] First adenoma observed at week 72 at 0 ppm.

[c] First hyperplasia observed at week 54 at 8000 ppm.

[+] Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

(n) Negative change from control.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Table 6: Historical Control Data for the Incidence of Thyroid C-Cell Tumors in Sprague-Dawley Strain Rats.

Tumor	Range (%) Males	Females
Carcinomas	0.0 - 5.2	0.0 - 2.9
Adenomas	1.8 - 10.6	3.3 - 10.0
Hyperplasia	4.3 - 20.0	4.3 - 16.9

iii. Liver (Table 7)

There was a slight dose-related increase in hepatocellular adenomas in males but the incidence was within the range of historical controls from Monsanto's EHL. The reported historical control incidence of hepatocellular carcinomas ranged from 0 to 6.7%, and that for hepatocellular adenomas ranged from 1.4 to 18.3%. There were no dose-related increases in the incidences of other hepatocellular lesions.

Table 7: Glyphosate - Sprague-Dawley Male Rats, Hepatocellular Tumor Rates* and Cochran-Armitage Trend and Fisher's Exact Test Results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20,000
Carcinomas	3/44	2/45	1/49	2/48[a]
(%)	(7)	(4)	(2)	(4)
p =	0.324	0.489(n)	0.269(n)	0.458(n)
Adenomas	2/44	2/45	3/49	7/48[b]
(%)	(5)	(4)	(6)	(15)
p =	0.016	0.683(n)	0.551	0.101
Adenoma/carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p =	0.073	0.486(n)	0.431(n)	0.245
Hyperplasia only	0/44	0/45	1/49[c]	0/48
(%)	(0)	(0)	(2)	(0)
p =	0.462	1.000	0.527	1.000

[a] First carcinoma observed at week 85 at 20,000 ppm.

[b] First adenoma observed at week 88 at 20,000 ppm.

[c] First hyperplasia observed at week 89 at 8000 ppm.

* Number of tumor-bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 55.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. If then $p < 0.05$.

Committee's interpretation: Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slightly increased occurrence of hepatocellular adenomas in males is not considered compound-related.

c. Nonneoplastic lesions

There were no compound-related nonneoplastic lesions.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

The HDT was 20,000 ppm which is the limit dose for carcinogenicity testing in rats. However, it appears that animals could have tolerated higher doses.

3. **Hogan, G. K. (1983). A chronic feeding study of glyphosate in mice. Unpublished report prepared by Bio/Dynamics Inc., dated July 21, 1983. Report No. 77-2061. EPA Acc. Nos. 251007 - 251009, and 251014.**

a. Experimental Design

Groups of 50 male and 50 female CD-1 mice were administered glyphosate in the diet at concentrations of 1000, 5000, or 30,000 ppm for 18 months.

b. Discussion of Tumor Data

Glyphosate produced an equivocal carcinogenic response in males characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

The Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee, in their meeting of February 11, 1985, tentatively classified glyphosate as a "Class C" carcinogen (report dated March 4, 1985). The kidney slides were reexamined by a consulting pathologist, and data were submitted indicating that an additional kidney tumor had been found in control males (the incidence in the control group was originally reported as 0/49 before the reexamination of the slides).

The Agency then requested that additional kidney sections from the mouse study be prepared and examined. The resultant microslides were examined by a number of pathologists. These examinations revealed no additional tumors, but confirmed the presence of the tumors identified in the original study report. The tumor in the control kidney was not present in any of the additional sections.

Because of the equivocal nature of the findings, the Toxicology Branch Ad Hoc Oncogenicity Peer Review Committee asked the expert assistance of the FIFRA Scientific Advisory Panel (SAP) in determining the proper Weight-of-the-Evidence classification of the study. After reviewing all the available evidence, the SAP, in their meeting of February 11-12, 1986, proposed that glyphosate be classified as "Class D," or having "inadequate animal evidence of oncogenicity." The principal reason for this assessment by SAP was their determination that, after adjusting for the greater survival in the high-dose mice compared to concurrent controls, no statistically significant pairwise differences existed, although the trend was significant. The SAP further noted that, although comparison of these findings to historical control incidences yielded a statistically significant result, this finding did not override the lack of pairwise significance of comparisons to concurrent controls.

The SAP determined that the carcinogenic potential of glyphosate could not be determined from existing data and proposed that rat and/or mouse studies be repeated in order to clarify these equivocal findings.

Committee's interpretation: In their meeting of June 26, 1991, the Health Effects Carcinogenicity Peer Review Committee concluded that despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females.

c. Nonneoplastic lesions:

Other nonneoplastic changes noted in high-dose male mice included centrilobular hypertrophy and necrosis of hepatocytes, chronic interstitial nephritis, and proximal tubule epithelial cell basophilia and hypertrophy in the kidneys of females. The no-observable-effect level (NOEL) for nonneoplastic chronic effects was the mid-dose level, 5000 ppm.

d. Adequacy of Dosing for Assessment of Carcinogenic Potential

Glyphosate was tested in this study at levels higher than the limit dose. Body weight gain in males of the high dose was 13, 17 and 27% less than the controls at 3, 12 and 24 months respectively. The decrease in body weight gains was statistically significant ($p < 0.01$). This effect was less obvious in females. The doses tested were considered adequate for the carcinogenic potential assessment of glyphosate.

E. Additional Toxicology Data on Glyphosate

1. Metabolism

When Sprague-Dawley rats were given a single oral dose of C-14 glyphosate, 30 to 36 percent of orally administered glyphosate was absorbed.

Data showed that less than 0.27 percent of the dose was expired as CO_2 within 24 hours. Glyphosate, per se, was the highest radiolabeled material found in the urine and feces. The minimum level of glyphosate extracted from urine and feces was 97.5 percent. Amino methyl phosphonic acid (AMPA) was found in the excreta of animals at levels of 0.2 to 0.3 percent and 0.2 to 0.4 percent in urine and feces, respectively. No detectable AMPA metabolite was found in intravenously dosed rats and high dose, orally dosed rats. There were no other metabolites of glyphosate found.

Based on analysis of radioactivity in urine and feces and using the "sigma-minus" plotting method, males and females had alpha half-lives of 2.11 and 7.52 hours and 5.00 to 6.44 hours, respectively. The beta half-lives of males and females in these groups ranged from 69.0 to 181 hours for males and 79.9 to 337 hours for females.

Less than 1 percent of the absorbed dose remains in tissues and organs, primarily bone. Repeated dosing with glyphosate

does not significantly change the metabolism, distribution, or excretion of glyphosate.

N-Nitrosoglyphosate (NNG)

The Agency has determined that carcinogenicity testing of nitroso contaminants will normally be required only in those cases in which the level of nitroso compounds exceeds 1.0 ppm [see "Pesticide Contaminated with N-nitroso Compounds, proposed policy 45 FR 42854 (June 25, 1980)"]. The levels of NNG in technical glyphosate have been examined by HED. The overall NNG content in individual samples of technical glypnosate analyzed at production plants is shown below:

Samples Analyzed		NNG Observed
No. Samples	Per cent	(ppb)
2035	92.6	< 1000
124	5.6	1000 - 1500
24	1.1	1500 - 2000
13	0.6	2000 - 3000
2	0.1	> 3000

The overall data show that 92.6 percent of the individual glyphosate samples analyzed contain less than 1.0 ppm (1000 ppb) of NNG. TB concluded that the NNG content of glyphosate technical is not toxicologically significant.

2. Mutagenicity

Glyphosate has been tested in several mutagenicity assays and found to be negative in each of the three categories recommended for evaluating genotoxic potential. The acceptable studies include the following: Salmonella assay, both with and without S-9, up to toxicity or 5000 ug/plate, in vivo cytogenetic assay in rat bone marrow up to 1000 mg/kg, mammalian gene HGPRT mutation assay in CHO cells in vitro both with and without S-9 up to toxic levels (10 mg/mL) and rec assay with B. subtilis up to 2000 ug/disk.

Unacceptable studies which were also negative included DNA repair in rat hepatocytes between 0.0000135 and 0.125 mg/ml, and a dominant lethal assay in mice up to 2000 mg/kg.

3. Developmental and Reproductive Toxicity

In rats, doses up to 3500 mg/kg/day showed no evidence of malformations. Evidence of developmental toxicity in the form of unossified sternebrae and decreased fetal body weight was noted in fetuses from the high dose (3500 mg/kg/day). This dose was also toxic to dams as evidenced by weight gain

deficits, altered physical appearance, and mortality during treatment. The developmental and maternal toxic NOEL for this study was 1000 mg/kg/day.

In rabbits, doses up to 350 mg/kg/day showed no evidence of malformations. The highest dose tested was toxic to does as evidenced by altered physical appearance and mortality. No treatment-related developmental effects were noted. The NOEL for maternal toxicity is 175 mg/kg/day and the NOEL for developmental toxicity is 350 mg/kg/day.

In a three-generation reproduction study in the rat, the only toxicologically significant finding was focal renal tubular dilation in the kidneys of male pups from the F_{3b} generation of high-dose dams (30 mg/kg/day). The NOEL for this effect was 10 mg/kg/day. No effects on fertility, reproductive, or other study parameters were noted.

4. Structure - Activity Relationships

Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and reported to be negative.

5. Acute, Subchronic and Chronic Feeding/ Oncogenicity Data

Glyphosate is not considered to be toxic to mammals (rat oral LD_{50} of 4320 mg/kg (both sexes), and a dermal LD_{50} greater than 7940 mg/kg in rabbits).

A 1-year chronic feeding study in dogs at 6/sex/dose was conducted using doses of 0, 20, 100, and 500 mg/kg/day, administered by capsule. The NOEL for the study was 500 mg/kg/day (HDT).

F. Weight of the Evidence Considerations

The Committee considered the following findings to be of significance regarding the weight-of-the-evidence determination of the carcinogenic potential of glyphosate.

1. Glyphosate was associated with increased incidences of pancreatic islet cell adenomas in male Sprague-Dawley rats at all treatment levels in comparison to the concurrent control group (Table 1). Although the low- (18%), mid- (10%) and high-dose group (15%) incidences exceeded the 1.8 to 8.5% range of historical controls from Monsanto's EHL data base, the pancreatic islet cell adenomas were not considered

compound-related for the following reasons: a) there was no statistically significant positive dose-related trend in the occurrence of these tumors or in the incidence of hyperplasia in males over the wide range of dosing (2000 to 20000 ppm), and b) there was no progression to carcinoma. Tertiary evidence from the open literature cited by the registrant showed a range of 0 to 17% for pancreatic islet cell adenomas in Sprague-Dawley male rats for unadjusted data. The incidence of pancreatic islet cell tumors for the two rat studies does not show a dose-related increase in adenomas or adenoma/carcinoma combined and is within the range of open literature control data for male Sprague-Dawley rats (0 to 17%) for unadjusted data.

No increased incidence of these tumors was observed in female rats in comparision to concurrent controls.

2. C-cell adenomas were slightly increased in male and female mid- and high-dose groups in the rat (Tables 4 and 5). Although C-cell adenomas slightly exceeded the historical control range for both sexes, there was no statistically significant trend or pairwise comparison with controls in males. In females, the incidence of C-cell adenomas was not statistically significant in the pairwise comparison with controls but had a statistically significant positive dose-related trend. However, there was no progression to carcinoma in a dose-related manner, and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. Therefore, the C-cell adenomas in males and females are not considered compound-related.

3. There was a slight dose-related increase in hepatocellular adenomas in male rats (Table 7), but the incidence was within the range of historical controls from Monsanto's EHL. This increase was not significant in the pair-wise comparison with controls and there was no progression from adenoma to carcinoma. The incidence of hyperplasia was not compound-related. There were no dose-related increases in the incidences of other hepatocellular lesions. Therefore, the increased incidence of hepatocellular adenomas in males was not considered compound-related.

4. Glyphosate produced an equivocal carcinogenic response in male mice characterized by an incidence of renal tubular neoplasms of 1/49, 0/49, 1/50, and 3/50 in the control, low-, mid-, and high-dose groups, respectively. No kidney tumors were found in females. Historical control data from 16 studies terminated between 1978 and 1982 provided by the testing laboratory indicated that the incidence of this type of tumor was found in 2/19 control groups (1/54 and 2/60, or a total of 3/1286).

Despite the fact that the incidence of renal tubular neoplasm in the high dose males exceeded that of historical controls, the biological significance of the findings was questionable because of: a) lack of significance in pairwise comparison with concurrent controls, b) there was no concurrent increase in non-neoplastic renal tubular lesions in male mice (e.g. tubular necrosis/regeneration, hyperplasia, hypertrophy ..etc), c) the examination of multiple sections of kidneys from all groups resulted in no additional neoplasms; this fact is particularly important since not only were the original sections closely scrutinized by more than one pathologist, but additional sections as well, and d) increased incidence in high dose group was very small compared to control considering the very high concentration which produced highly significant reduction in body weight gain in males. Furthermore, the increased incidence of chronic interstitial nephritis in males is not relevant to the tubular neoplasms. There was actually a decrease in renal tubular epithelial changes (basophilia and hyperplasia) in males, and although there was a dose-related increase in these changes in female mice, no tubular neoplasms were observed in females. Overall, the Peer Review Committee did not feel that this lesion was compound-related.

5. Glyphosate was tested up to the limit dose in the rat, and up to levels higher than the limit dose in mice.

6. There was no evidence of genotoxicity for glyphosate.

7. Currently there are no structurally related pesticides registered by the Agency which resemble glyphosate. A nonregistered pesticide, sulfosate, has been reviewed for carcinogenic potential in mice and rats and was reported to be negative.

G. <u>Classification</u>:

Considering criteria contained in EPA Guidelines (FR 51:33992-34003, 1986] for classifying a carcinogen, the Committee concluded that Glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans), based on lack of convincing carcinogenicity evidence in adequate studies in two animal species.

It should be emphasized, however, that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

END

Bill Dykstra (46)

Glyphosate/Tox

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Releasable

FEB 24 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Transmittal of the Final FIFRA Scientific Advisory Panel Reports on the February 11-12, 1986 Meeting

TO: Steven Schatzow, Director
Office of Pesticide Programs (TS-766)

The above mentioned meeting of the FIFRA Scientific Advisory Panel (SAP) was an open meeting held in Arlington, Virginia to review the following topics:

(1) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Glyphosate;

(2) A set of scientific issues in connection with the Agency's proposed action on the non-wood uses of Pentachlorophenol as set forth in the Position Document 4;

(3) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Oryzalin;

(4) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Amitraz;

(5) A set of scientific issues being considered by the Agency in connection with the Registration Standard for Acephate;

(6) A set of scientific issues being considered by the Agency in connection with Subdivision U of the Pesticide Assessment Guidelines.

Please find attached the SAP's final reports on the six issues discussed at the meeting.

Stephen L. Johnson, Executive Secretary
FIFRA Scientific Advisory Panel (TS-769)

Attachments

cc: Panel Members
John A. Moore
James Lamb
Al Heier
Susan Sherman
John Melone
Douglas Campt
EPA Participants

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

SCIENTIFIC ADVISORY PANEL

A Set of Scientific Issues Being Considered by the Agency in Connection with the Registration Standard for Glyphosate

---

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) has completed review of the data base supporting the Environmental Protection Agency's (EPA) decision to reclassify Glyphosate as a class C (possible human) carcinogen. The review was conducted in an open meeting held in Arlington, Virginia, on February 11, 1986. All Panel members, except Dr. Thomas W. Clarkson, were present for the review. In addition, Dr. David Gaylor, Director of the Biometry Staff at the National Center for Toxicological Research, served as an ad hoc member of the Panel.

Public notice of the meeting was published in the Federal Register on Friday, January 17, 1986 (Citation 51-FR2568).

Oral statements were received from staff of the Environmental Protection Agency and from Mr. Robert Harness and Dr. Timothy Long of Monsanto Company.

In consideration of all matters brought out during the meeting and careful review of all documents presented by the Agency, the Panel unanimously submits the following report.

REPORT OF SAP RECOMMENDATIONS

General Comments on Carcinogen Classification

The Panel concurs that it is necessary to categorize chemicals as to their apparent carcinogenic risk to man. The Panel is concerned that the categories outlined in the Agency's Cancer Guidelines are somewhat limited in scope. For only a small number of specific chemicals is there epidemiologic evidence of their carcinogenicity in man, either sufficient evidence (Group A) or limited evidence (Group B-1). Thus, most chemicals that are carcinogenic for animals have been placed in Groups B-2 and C. Category D has apparently not been used. The Panel urges the Agency to attempt to develop a more discriminatory classification scheme.

Glyphosate

The Agency requested the Panel to focus its attention upon a set of issues relating to the pesticide Glyphosate. There follows a list of the issues and the SAP's response to each question.

1. Based on the Agency's weight of the evidence assessment with emphasis on the mouse kidney tumors, the Agency has classified Glyphosate as a class C (possible human) carcinogen. The Agency specifically requests any comment that the Panel may wish to present with regard to its assessment of the weight of evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines.

2. The Agency requests also that the Panel consider what weight should be given to this marginal increase in kidney tumors, the importance of this type of tumor in the assessment of the carcinogenicity of Glyphosate, and the weight placed on historical and concurrent controls for this type of evaluation.

Panel Response:

In the instance of Glyphosate, the Panel concurs that the data on renal tumors in male mice are equivocal. Only small numbers of tumors were found in any group, including those at the highest dose which appear to have exceeded the maximal tolerated dose. The vast majority of the pathologists, who examined the proliferative lesion in the male control animal, agreed that the lesion represented a renal adenoma. Therefore, statistical analysis of the data should utilize this datum. In addition, the statistical analysis shall be age-adjusted; when this is done, no oncogenic effect of Glyphosate is demonstrated using concurrent controls. Nevertheless, the occurrence of three neoplasms in high dose male mice is unusual and using historical controls is statistically highly significant. Furthermore, categorization of the oncogenic risk of Glyphosate is complicated by the fact that doses used in the rat study do not appear to have reached the maximal tolerated dose. Under these circumstances, the Panel does not believe that it is possible to categorize Glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity for humans). The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions.

Regarding the issue of using historical or concurrent controls, the Panel believes that this has to be decided on a case-by-case basis. For Glyphosate, the historical control data support that there may be reason for concern. However, the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.

FOR THE CHAIRMAN

Certified as an accurate report of Findings:

Stephen L. Johnson
Executive Secretary
FIFRA Scientific Advisory Panel

Date: 2/24/86

Message

From: Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]
Sent: 10/8/2015 10:53:46 AM
To: STURMA Juergen [Juergen.STURMA@efsa.europa.eu]
Subject: RE: GLyphosate

Dear Juergen

Thank you so much for the information.

Regards

JR
Jess owland,
Deputy Director
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
703-308-2719

From: STURMA Juergen [mailto:Juergen.STURMA@efsa.europa.eu]
Sent: Thursday, October 08, 2015 1:54 AM
To: Rowland, Jess
Cc: EFSA PESTICIDES PEER REVIEW; COURT MARQUES Daniele
Subject: RE: GLyphosate

Dear Jess,

After the adoption of our conclusion, we have to undergo the step of sanitisation before we can publish the documents on our website. For the conclusion, I guess, this might not take much longer than 2 weeks. So, we expect the conclusion to be available to the public by mid-November. I am sorry, but for the time being, I cannot be more precise.

Let me know, if additional information on the process is needed.

Best regards

Jürgen

Jürgen Sturma
Scientific Officer
Pesticides / Regulated Products

efsa
European Food Safety Authority
Via Carlo Magno 1A
43126 Parma (Italy)
Tel. +39 0521 036 655
www.efsa.europa.eu

From: COURT MARQUES Daniele
Sent: 07 October 2015 21:26
To: Rowland, Jess
Cc: EFSA PESTICIDES PEER REVIEW; STURMA Juergen
Subject: Re: GLyphosate

Dear Jess,

Thank you for the information, I include in cc Juergen who is coordinating the peer review. He will be able to give you more precise information regarding the publication.

Kind regards,
Danièle

Enviado do meu iPhone

No dia 7 de out de 2015, às 20:48, Rowland, Jess <Rowland.Jess@epa.gov> escreveu:

> Dear Daniele
>
> OPP is in the process of conducting risk assessment on glyphosate, which will include the re-evaluation of carcinogenicity. We would like to release our risk assessment at the same time when EFSA conclusion is published. I see you plan to release your report in November; can you give some approximate date of the release so we can make our plans.
>
> Thank you and kind regards
>
> Jess Rowland,
> Deputy Director
> Health Effects Division
> Office of Pesticide Programs
> U.S. Environmental Protection Agency
> 703-308-2719
>
> **From:** COURT MARQUES Daniele [mailto:Daniele.COURTMARQUES@efsa.europa.eu]
> **Sent:** Friday, October 02, 2015 3:32 AM
> **To:** Rowland, Jess
> **Cc:** EFSA PESTICIDES PEER REVIEW; STURMA Juergen; PRAS.secretariat
> **Subject:** RE: GLyphosate
>
> Dear Jess,
>
> Indeed your participation was very helpful, and we were glad to have you on board, thank you!
>
> The report of the meeting will be published together with the EFSA conclusion (as background documents in the peer review report) that is expected to be in November.
> However if you need to receive the minutes earlier, I can send them to you under embargo; kindly let me know.

Kind regards,
Danièle

Danièle Court Marques

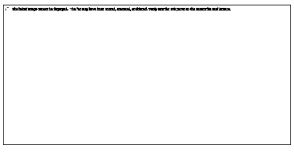
Pesticides Unit - Toxicology
Scientific Evaluation of Regulated Products Directorate
European Food Safety Authority

Via Carlo Magno 1/A I-43126 Parma
Tel : +39 0521 036 847
Fax : +39 0521 036 0847
Daniele.COURTMARQUES@efsa.europa.eu
http://www.efsa.europa.eu

From: CIAULA Maria **On Behalf Of** PRAS.secretariat
Sent: 02 October 2015 09:05
To: Rowland, Jess
Cc: COURT MARQUES Daniele; EFSA PESTICIDES PEER REVIEW
Subject: RE: GLyphosate

Dear Jess,
Thank you very much for your message, I'm really happy about your feedback.
With regard to your question, I'm copying my colleague Danièle and the Peer Review scientific coordination team who will be able to answer you.
Kind regards
Maria

Maria CIAULA
Administrative assistant
PESTICIDES
REPRO Department



Via Carlo Magno 1A
43126 Parma (Italy)
Tel: +39. 0521. 036 694
www.efsa.europa.eu
twitter.com/EFSA_EU **<image001.jpg.secure>**
youtube.com/EFSAchannel **<image002.jpg.secure>**

From: Rowland, Jess [mailto:Rowland.Jess@epa.gov]
Sent: 01 October 2015 18:19
To: PRAS.secretariat
Subject: GLyphosate

HI Maria

Thank you for the opportunity to participate in the EFSA meeting. I hope I was helpful.
That was very interesting and I learned a lot on the review and evaluation of the studies by the different countries.

What will be next step? If there is a report, can you tell me when that would be coming out?

Regards

Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

Message

From: Rowland, Jess [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=F726A9239C924C08B38C1A0940CCFD5E-JESS ROWLAND]
Sent: 11/4/2015 5:58:50 PM
To: May, Brenda [May.Brenda@epa.gov]
Subject: RE: Press: The Intercept about glyphosate

Here is the link

https://theintercept.com/2015/11/03/epa-used-monsanto-funded-research/

JR
Jess Rowland,
Deputy Director
Health Effects Division
703-308-2719

From: May, Brenda
Sent: Wednesday, November 04, 2015 9:13 AM
To: Rowland, Jess <Rowland.Jess@epa.gov>
Subject: Re: Press: The Intercept about glyphosate

The article wasn't attached. Did you get it?

Sent from my iPhone

On Nov 4, 2015, at 6:32 AM, Rowland, Jess <Rowland.Jess@epa.gov> wrote:

> Going to be fun when our PRA gets out 😺
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> **From:** "Jones, Jim" <Jones.Jim@epa.gov>
> **Date:** November 4, 2015 at 5:28:53 AM EST
> **To:** "Vogel, Dana" <Vogel.Dana@epa.gov>
> **Cc:** "Rowland, Jess" <Rowland.Jess@epa.gov>, "Strauss, Linda" <Strauss.Linda@epa.gov>, "Housenger, Jack" <Housenger.Jack@epa.gov>, "Mojica, Andrea" <Mojica.andrea@epa.gov>, "Wise, Louise" <Wise.Louise@epa.gov>
> **Subject: Fwd: Press: The Intercept about glyphosate**
>
> Dana, The attached article gives a roadmap for the types of critiques we need to be prepared to respond to for glyphosate. Let's be ready to respond to these types of arguments Jim

Sent from my iPhone

Begin forwarded message:

From: "Strauss, Linda" <Strauss.Linda@epa.gov>
Date: November 3, 2015 at 5:07:35 PM EST
To: "Jones, Jim" <Jones.Jim@epa.gov>, "Wise, Louise" <Wise.Louise@epa.gov>, "Sterling, Sherry" <Sterling.Sherry@epa.gov>, "Mojica, Andrea" <Mojica.andrea@epa.gov>, "Dunton, Cheryl" <Dunton.Cheryl@epa.gov>
Subject: Press: The Intercept about glyphosate

From: Purchia, Liz
Sent: Tuesday, November 03, 2015 4:28 PM
To: Daguillard, Robert <Daguillard.Robert@epa.gov>; Conger, Nick <Conger.Nick@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dix, David <Dix.David@epa.gov>; Robbins, Jane <Robbins.Jane@epa.gov>; Wooge, William <Wooge.William@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Harrison, Melissa <Harrison.Melissa@epa.gov>
Subject: RE: NICK ACTION: FOLLOW-UP: DDL TODAY The Intercept about glyphosate

https://theintercept.com/2015/11/03/epa-used-monsanto-funded-research/

From: Daguillard, Robert
Sent: Thursday, October 29, 2015 10:20 AM
To: Conger, Nick <Conger.Nick@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dix, David <Dix.David@epa.gov>; Robbins, Jane <Robbins.Jane@epa.gov>; Wooge, William <Wooge.William@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Harrison, Melissa <Harrison.Melissa@epa.gov>; Purchia, Liz <Purchia.Liz@epa.gov>
Subject: RE: NICK ACTION: FOLLOW-UP: DDL TODAY The Intercept about glyphosate

Hullo Nick

I haven't spoken with the reporter, but I've handled part of her inquiry – keep in mind this is a follow-up. I expect she'll paint the regulatory regime for glyphosate and, perhaps, pesticides in general, as lax and exceedingly friendly to industry. Her questions certainly suggest as much.

Robert Daguillard
Office of Media Relations
U.S. Environmental Protection Agency

Washington, DC
+1 (202) 564-6618 (o)
+1 (202) 360-0476 (cel)
<< OLE Object: Picture (Device Independent Bitmap) >>

From: Conger, Nick
Sent: Thursday, October 29, 2015 10:16 AM
To: Daguillard, Robert <Daguillard.Robert@epa.gov>; Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Dix, David <Dix.David@epa.gov>; Robbins, Jane <Robbins.Jane@epa.gov>; Wooge, William <Wooge.William@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Harrison, Melissa <Harrison.Melissa@epa.gov>; Purchia, Liz <Purchia.Liz@epa.gov>
Subject: RE: NICK ACTION: FOLLOW-UP: DDL TODAY The Intercept about glyphosate

Thanks Robert. Did you speak with this reporter? The Intercept is Glenn Greenwald's blog and I know they typically looking for stories within stories.

I think these responses are fine, but flagging for Melissa's and Liz's awareness. If you don't hear back from any of us by 11am, please proceed with responding. But if you have any context or insight into her story, let us know.

Nick Conger
Deputy Press Secretary
U.S. Environmental Protection Agency
Office: (202) 564-6287
Cell: (202) 412-2655

From: Daguillard, Robert
Sent: Thursday, October 29, 2015 8:46 AM
To: Strauss, Linda <Strauss.Linda@epa.gov>; Conger, Nick <Conger.Nick@epa.gov>
Cc: Dix, David <Dix.David@epa.gov>; Robbins, Jane <Robbins.Jane@epa.gov>; Wooge, William <Wooge.William@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: NICK ACTION: FOLLOW-UP: DDL TODAY The Intercept about glyphosate

Thank you, Linda

Nick, for your approval. Please find the questions from reporter Sharon Lerner from The Intercept; and the response, approved by OCSPP's Jim Jones. The reporter's deadline is today AM.

Thanks, R.

I wanted to confirm that glyphosate will NOT be moving ahead to Tier 2 testing.

As stated in the glyphosate Endocrine Disruptor Screening Program (EDSP) Tier 1 Screening Result document:

"Based on weight of evidence considerations, mammalian or wildlife EDSP Tier 2 testing is not recommended for glyphosate since there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways."

The glyphosate EDSP Weight of Evidence document can be found here:

http://www2.epa.gov/ingredients-used-pesticide-products/weight-evidence-edsp-glyphosate

What is the timeframe for the 18 pesticides that will be moving ahead to Tier 2 testing?

EPA is currently finalizing the Information Collection Request (ICR) as mandated by the Paperwork Reduction Act that will allow EPA to issue EDSP Tier 2 Testing orders.

Were the EDC reviews done by a panel? If so, can I see a list of the members for the glyphosate review panel?

The EDSP Tier 1 Screening weight of evidence conclusions were developed internally by EPA scientists and were not reviewed by an external body or panel. The methods and processes by which the EPA developed these determinations have been evaluated by external panels (*e.g.*, FIFRA Scientific Advisory Panel) and international groups (*e.g.*, Organisation for Economic Co-operation and Development (OECD)).

Some have said that EPA's review process, whether for EDC reviews or reregistration of pesticides, favors industry because it relies so heavily on data provided by companies. How do you ensure these processes are fair?"

The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA, sections 3 and 4), the primary federal law governing the regulation of pesticides, makes clear that EPA shall require the submission of studies from pesticide registration applicants to support registration of pesticide products. Congress placed this obligation on the pesticide registrant rather than requiring taxpayers to fund data development.

To ensure the quality and integrity of data submitted to the agency, EPA regulations set forth good laboratory practices for labs conducting studies that are intended to support applications for registration of pesticide products. EPA's Good Laboratory Practice Standards compliance monitoring program helps ensure the quality and integrity

of test data submitted to the Agency in support of a pesticide product registration under FIFRA. EPA also conducts inspections of these laboratories and data audits to monitor compliance.

Once studies are submitted to the agency, EPA scientists analyze the data to ensure that the design of the study is appropriate and that the data have been collected and analyzed accurately. In addition to registrant-submitted studies, EPA scientists review pesticide studies from peer-reviewed scientific journals and data from a wide variety of sources. Agency scientists identify hazards and characterize risks using the best data available for their review.

How many chemicals have been reviewed through the endocrine screening program thus far?

67 chemicals have been issued EDSP Tier 1 screening orders. As a result, the order recipients of 15 chemicals chose not to develop the screening data (and subsequently withdrew from the market). A status table of the EDSP List 1 orders can be found here:

http://www2.epa.gov/endocrine-disruption/status-endocrine-disruptor-screening-program-tier-1-test-orders-list-1

The remaining 52 chemicals complied with the issued EDSP Tier 1 orders and submitted the appropriate data. The 52 EDSP Tier 1 Screening Assessments can be found here:

http://www2.epa.gov/ingredients-used-pesticide-products/endocrine-disruptor-screening-program-tier-1-assessments

However, we are now using a new approach to screen chemicals faster, cheaper and to reduce animal testing. Over 1,800 chemicals have been partially screened for estrogenic bioactivity based on estrogen receptor model data. More information on the estrogen model can be found here:

http://www2.epa.gov/endocrine-disruption/use-high-throughput-assays-and-computational-tools-endocrine-disruptor

Have any of those reviews concluded that the chemical in question was an endocrine disruptor?

The determination that a chemical does or is not likely to have potential bioactivity in the endocrine system (*i.e.*, estrogen, androgen, or thyroid hormone pathways) will be made on a Weight of Evidence (WoE) basis, taking into account all available data on the compound including data from the Tier 1 screening assays and other scientifically relevant information.The fact that a substance is bioactive in a hormone pathway based on Tier 1 screening, however, does not mean that when the substance is used, it will cause endocrine disruption or adverse effects in humans or wildlife. The ultimate purpose of the EDSP is to provide information that will allow the Agency to evaluate the risks

associated with the use of a chemical and take appropriate steps to mitigate any risks of concern.

Robert Daguillard
Office of Media Relations
U.S. Environmental Protection Agency
Washington, DC
+1 (202) 564-6618 (o)
+1 (202) 360-0476 (cel)
<< OLE Object: Picture (Device Independent Bitmap) >>

From: Strauss, Linda
Sent: Thursday, October 29, 2015 7:56 AM
To: Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Daguillard, Robert <Daguillard.Robert@epa.gov>
Cc: Dix, David <Dix.David@epa.gov>; Robbins, Jane <Robbins.Jane@epa.gov>; Wooge, William <Wooge.William@epa.gov>
Subject: FW: LINDA ACTION: FOLLOW-UP: The Intercept about glyphosate

Cathy/Robert, here you go (OKed by Jim).
Bill/Jane, thanks!!

Linda

I wanted to confirm that glyphosate will NOT be moving ahead to Tier 2 testing.

As stated in the glyphosate Endocrine Disruptor Screening Program (EDSP) Tier 1 Screening Result document:

"Based on weight of evidence considerations, mammalian or wildlife EDSP Tier 2 testing is not recommended for glyphosate since there was no convincing evidence of potential interaction with the estrogen, androgen or thyroid pathways."

The glyphosate EDSP Weight of Evidence document can be found here:

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Were the EDC reviews done by a panel? If so, can I see a list of the members for the glyphosate review panel?

The EDSP Tier 1 Screening weight of evidence conclusions were developed internally by EPA scientists and were not reviewed by an external body or panel. The methods and processes by which the EPA developed these determinations have been evaluated by external panels (*e.g.*, FIFRA Scientific Advisory Panel) and international groups (*e.g.*, Organisation for Economic Co-operation and Development (OECD)).

Some have said that EPA's review process, whether for EDC reviews or reregistration of pesticides, favors industry because it relies so heavily on data provided by companies. How do you ensure these processes are fair?"

The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA, sections 3 and 4), the primary federal law governing the regulation of pesticides, makes clear that EPA shall require the submission of studies from pesticide registration applicants to support registration of pesticide products. Congress placed this obligation on the pesticide registrant rather than requiring taxpayers to fund data development.

To ensure the quality and integrity of data submitted to the agency, EPA regulations set forth good laboratory practices for labs conducting studies that are intended to support applications for registration of pesticide products. EPA's Good Laboratory Practice Standards compliance monitoring program helps ensure the quality and integrity of test data submitted to the Agency in support of a pesticide product registration under FIFRA. EPA also conducts inspections of these laboratories and data audits to monitor compliance.

Once studies are submitted to the agency, EPA scientists analyze the data to ensure that the design of the study is appropriate and that the data have been collected and analyzed accurately. In addition to registrant-submitted studies, EPA scientists review pesticide studies from peer-reviewed scientific journals and data from a wide variety of sources. Agency scientists identify hazards and characterize risks using the best data available for their review.

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http://www2.epa.gov/ingredients-used-pesticide-products/endocrine-disruptor-screening-program-tier-1-assessments

However, we are now using a new approach to screen chemicals faster, cheaper and to reduce animal testing. Over 1,800 chemicals have been partially screened for estrogenic bioactivity based on estrogen receptor model data. More information on the estrogen model can be found here:

http://www2.epa.gov/endocrine-disruption/use-high-throughput-assays-and-computational-tools-endocrine-disruptor

Have any of those reviews concluded that the chemical in question was an endocrine disruptor?

The determination that a chemical does or is not likely to have potential bioactivity in the endocrine system (*i.e.*, estrogen, androgen, or thyroid hormone pathways) will be made on a Weight of Evidence (WoE) basis, taking into account all available data on the compound including data from the Tier 1 screening assays and other scientifically relevant information.The fact that a substance is bioactive in a hormone pathway based on Tier 1 screening, however, does not mean that when the substance is used, it will cause endocrine disruption or adverse effects in humans or wildlife. The ultimate purpose of the EDSP is to provide information that will allow the Agency to evaluate the risks associated with the use of a chemical and take appropriate steps to mitigate any risks of concern.

From: Daguillard, Robert
Sent: Tuesday, October 27, 2015 2:47 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>
Cc: Milbourn, Cathy <Milbourn.Cathy@epa.gov>
Subject: LINDA ACTION: FOLLOW-UP: The Intercept about glyphosate

Linda, some follow-up questions from Rachel Lerner on Glyphosate. I'm trying to clarify her deadline info.

"I found this page on your site, which was very helpful and answered most of the questions above.

I do have a few other questions, which I've listed below and would love a response to by the end of Thursday, when I'll be filing my piece:

1) I wanted to confirm that glyphosate will NOT be moving ahead to Tier 2 testing.

2) What is the timeframe for the 18 pesticides that will be moving ahead to Tier 2 testing?

3) Were the EDC reviews done by a panel? If so, can I see a list of the members for the glyphosate review panel?

4) Some have said that EPA's review process, whether for EDC reviews or reregistration of pesticides, favors industry because it relies so heavily on data provided by companies. How do you ensure these processes are fair?"

Robert Daguillard
Office of Media Relations
U.S. Environmental Protection Agency
Washington, DC
+1 (202) 564-6618 (o)
+1 (202) 360-0476 (cel)
<< OLE Object: Picture (Device Independent Bitmap) >>

From: Jones, Enesta
Sent: Friday, October 23, 2015 3:05 PM
To: Strauss, Linda <Strauss.Linda@epa.gov>; Dunton, Cheryl <Dunton.Cheryl@epa.gov>
Cc: Sisco, Debby <Sisco.Debby@epa.gov>; Overstreet, Anne <overstreet.anne@epa.gov>; Keltz, Colleen <Keltz.Colleen@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>; Dunton, Cheryl <Dunton.Cheryl@epa.gov>; Milbourn, Cathy <Milbourn.Cathy@epa.gov>; Daguillard, Robert <Daguillard.Robert@epa.gov>; Jones, Enesta <Jones.Enesta@epa.gov>
Subject: FOLLOW-UP: The Intercept about glyphosate

Hi,
She has follow up; **DDL: 10/27.**

I have two additional questions relating to the endocrine screening program, and the recently released review of glyphosate in particular. (Here is the document I'm referring to: http://www2.epa.gov/sites/production/files/2015-06/documents/glyphosate-417300_2015-06-29_txr0057175.pdf)

How many chemicals have been reviewed through the endocrine screening program thus far?

Have any of those reviews concluded that the chemical in question was an endocrine disruptor?

Enesta Jones
U.S. EPA, Office of Media Relations
Desk: 202.564.7873
Cell: 202.236.2426

On Oct 23, 2015, at 11:12 AM, Strauss, Linda <Strauss.Linda@epa.gov> wrote:

Here you go, Enesta.

Linda

From: Strauss, Linda
Sent: Thursday, October 22, 2015 3:58 PM
To: Jones, Jim <Jones.Jim@epa.gov>; Wise, Louise <Wise.Louise@epa.gov>; Sterling, Sherry <Sterling.Sherry@epa.gov>; Mojica, Andrea <Mojica.andrea@epa.gov>
Subject: Due today - FW: Press inquiry from The Intercept about glyphosate

Question 1: I also have a few questions about the re-registration of glyphosate: What's the time-table? i.e. is there a date when it must be completed?

Response:. EPA will publish the registration review preliminary risk assessments for glyphosate in the next few months for a 60-day public comment period. It will be available in the glyphosate docket (docket #: EPA-HQ-OPP-2009-0361) on regulations.gov. We intend to issue a proposed interim decision for glyphosate in 2016 and an interim final decision in 2017, which will be a comprehensive review of everything except for the endangered species review. The final decision will come after the Services finish their consultation on endangered species.

Background: In the registration review program, the agency is reviewing each registered pesticide every 15 years to determine whether it continues to meet the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) standard for registration. Therefore, if a pesticide was registered in October 2007, it must be reregistered by October 2022.

Question 2: How many studies are being considered in re-registration? And are they all available on regulations.gov or do I need to come to DC to see them?

Response: EPA reviewed a large volume of studies submitted to the agency and drawn from open literature. These studies ranged across a number of areas such as ecotoxicity, ecological fate, human health epidemiology, and cancer. The preliminary risk assessments will include bibliographic information for each study reviewed. The public will be able to search for studies from the open literature by using the listed references. Studies submitted to EPA by registrants are available to the public under the Freedom of Information Act. For information on how to obtain access to those studies, visit: http://www2.epa.gov/foia. In general, EPA's reviews (data evaluation records) of registrants' proprietary glyphosate studies are available via EPA's Chemical Search website: http://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1.

From: Sharon Lerner <fastlerner@gmail.com>
Date: October 19, 2015 at 11:32:57 AM EDT
To: "Milbourn, Cathy" <Milbourn.Cathy@epa.gov>
Subject: Re: Press Inquiry about glyphosate

Cathy, I also have a few questions about the re-registration of glyphosate:
First, what's the time-table? i.e. is there a date when it must be completed?
Second, how many studies are being considered in re-registration? And are they all available on regulations.gov?
Thanks so much,
Sharon

On Mon, Oct 19, 2015 at 11:00 AM, Sharon Lerner <fastlerner@gmail.com> wrote:
Yes, thanks, Cathy. I'm looking at it now. Do you know if there's anything available in DC that's not online?

On Oct 19, 2015, at 10:59 AM, Milbourn, Cathy <Milbourn.Cathy@epa.gov> wrote:

Hi Sharon,

The docket for glyphosate should be on line. Did you see it in regs.gov?

Catherine C. Milbourn
U.S. EPA HQ
Office of the Administrator
Office of Media Relations
202-564-7849 (office)
202-420-8648 (mobile)

Milbourn.cathy@epa.gov

From: Sharon Lerner [mailto:fastlerner@gmail.com]
Sent: Monday, October 19, 2015 9:44 AM
To: Milbourn, Cathy
Subject: Press Inquiry about glyphosate

Hi Cathy-
I'm writing a story about glyphosate and would like to arrange to come to DC and view the public docket for it. Can you please let me know the soonest date available to do this?
Thanks,
Sharon

Sharon Lerner
Reporter, The Intercept
718-877-5236
@fastlerner